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REVIEW PAPER

Consequences of premature ovarian insufficiency on women's sexual health

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Abstract

Premature ovarian insufficiency (POI) is defined by amenorrhoea and decreased serum levels of oestrogens associated with increased serum gonadotropins concentrations before the age of 40 years. Patients suffering from POI present with irregular menses, either secondary or (less common) primary amenorrhoea, and subfertility. POI affects approximately 1 in 100 women by the age 40 years and 0.1% by 30 years of age. Both spontaneous and iatrogenic causes may induce POI, although up to 90% of POI cases are idiopathic. Impairment of sexual function is a common problem affecting women suffering from POI. Premature loss of gonadal function is particularly traumatic in young women and affects many aspects of physical and social life. POI patients suffer from genital pain due to vaginal dryness and diminished sexual arousal. Additionally, POI patients report increased anxiety, depressed mood, and have impaired interactions with their peers, which leads to feeling less feminine and having decreased self-esteem. Moreover, they have significantly decreased physical and psychological well-being when compared to age-matched controls. Systemic hormonal replacement therapy and topical oestrogen therapy as well as vaginal moisturisers may be used in the treatment of POI patients' sexual impairment.

Key words: premature ovarian insufficiency, early menopause, hormonal replacement therapy, sexual life.

Introduction

Premature ovarian insufficiency (POI) is a disorder characterised by amenorrhoea and and decreased serum levels of oestrogens associated with increased serum gonadotropins concentrations before the age of 40 years. Patients suffering from POI present with irregular menses, either secondary or (less common) primary amenorrhoea, and subfertility. This condition leads to decreased concentration of circulating oestrogens. Moreover, patients may suffer from hot flushes and other symptoms associated with classical postmenopausal state, such as mood disturbances, difficulties in concentration, fatigue, cognitive or sexual impairment, urinary incontinence, vulvovaginal atrophy, and weight gain [1].

Although up to 90% of POI cases are idiopathic, the remainder develop as a result of genetic, enzymatic, and autoimmune causes. Improved survival rates following childhood malignancies contribute to an increasing number of chemo- or radiotherapy-associated POIs, while the incidence of idiopathic POI appears to remain stable [2].

POI affects approximately 1 in 100 women by the age of 40 years and 0.1% by 30 years [2]. A diagnosis of POI can be suspected after at least 3-4 months of menstrual irregularities (oligomenorrhoea or amenorrhoea) and two FSH levels in the menopausal range, assessed on two separate occasions at least four weeks apart before the age of 40 years [3].

Impairment of sexual function is a common problem affecting women suffering from POI. Premature loss of gonadal function is particularly traumatic in young women and affects many aspects of physical and social life. Such complex physical and psychological difficulties often lead to the loss of self-confidence and self-image. Women suffering from POI report feeling less feminine, increased anxiety, depressed mood, and having impaired interactions with their peers [4].

Sexual function in premature ovarian insufficiency patients

It is estimated that hormonal imbalance associated with POI affects a women's sexual identity, sexual function, and sexual relationships. Decreased concentration of oestrogens and androgens contribute to reduced desire and arousal, vaginal dryness, difficulties in achieving orgasm, and painful intercourse [4]. Women suffering from POI present with declining sexual performance when compared to healthy controls [5]. Hypoestrogenism contributes to decreased clitoral response, impaired reactivity of vaginal walls, as well as decreased vaginal contractions. Moreover, impaired lubrication and

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vaginal atrophy leads to dyspareunia, and injuries following sexual intercourse [6]. It is noteworthy that POI patients often have hormonal vaginal cytology and vaginal pH results within acceptable norms, but poor vaginal health index (VHI) results. Nevertheless, decreased VHI in POI does not correlate with intensity of pain during intercourse and degree of lubrication [5].

Extent of sexual impairment depends largely on aetiology, life cycle stage, factors personal to the woman, and family/societal influences [7]. Additionally, factors modulating the influence of POI on sexual activity are age, sexual health of the partner, parity, and quality of intimacy in previous and present relationships [7].

A study of 81 POI women estimated that patients suffering from POI had significantly fewer sexual fantasies and masturbated less frequently, when compared to controls. Moreover, patients suffered from decreased lubrication and associated increased genital pain and diminished sexual arousal. Nevertheless, desire for sexual contact and frequency of contact with their partner was not impaired [8]. Another study conducted on 80 POI patients demonstrated that almost all domains of sexual life included in the Female Sexual Function Index (FSFI), such as arousal, lubrication, orgasm, satisfaction, and pain, were affected. Desire was the only domain in which scores were not significantly decreased; however, the POI group scored much lower in this domain than did the control group. Psychological-based domains, such as desire, sexual response, and arousal, were considered to have a stronger impact on the total index of sexual function. The domains of arousal and desire, by far, contributed the most (41%) [6]. These results were confirmed in a second study of 58 POI [9]. Another cross-sectional observational study of 25 POI patients revealed that POI patients are less sexually responsive, have lower libido, and suffer from dyspareunia more often than healthy premenopausal controls [10].

Regarding surgical menopause, in another cross-sectional survey, Dennerstein *et al.* determined that abrupt premature menopause due to hysterectomy and bilateral oophorectomy is associated with a greater prevalence of hypoactive sexual desire disorder (HSDD). They found that these women suffered from lower sexual desire, and diminished sexual arousal and pleasure. All these factors were associated with negative self-esteem and decreased relationship satisfaction [11]. Nevertheless, it is reported that surgical premature menopause is associated with the lowest overall influence on sexual life among the different causes of POI [10].

Premature ovarian insufficiency and quality of life

A case-control study of 58 POI women reported decreased scores in psychological and physical health domains in the World Health Organisation Quality of Life questionnaire (WHOQOL-100), when compared to healthy controls. In contrast, there was no difference in the social relationships, quality of life in general, health in general, and environment domains. The POI patient group reported a higher frequency of negative feelings such as despair, anxiety, and depression when compared to controls (p = 0.015) [12]. Similarly, in another case-control study evaluating the quality of life and sexual function of 80 POI women, it was estimated that POI patients had significantly decreased physical and psychological well-being when compared to age-matched controls. Impairment of the sexual life of those patients was found to have a significant impact on their social interactions. It is worth noting that of all sexual life parameters assessed, psychological domains, such as orgasm and sexual satisfaction, as opposed to physical ones (pain and lubrication), were most strongly correlated with quality of life. FSFI was also positively correlated with quality of life [13].

Androgens in premature ovarian insufficiency

It is well established that POI patients suffer from androgen deficiency due to atrophy of the ovarian cortex. Although there exist certain exceptions in the literature, most studies have demonstrated abnormal free testosterone and androstenedione concentrations in patients with POI when compared to controls [14, 15]. This difference is particularly pronounced in chemotherapy-induced POI patients, where the abrupt decreases in serum androgen concentrations (compared to the more gradual fluctuations seen physiologically) can lead to difficulties in sexual life. Women who underwent oophorectomy at a young age similarly become hypoandrogenic due to insufficient ovarian androgen production [15]. In the study involving 81 POI patients, van der Stege *et al.* demonstrated decreased concentration of total testosterone and androstenedione in a POI patient group when compared to healthy age-matched controls. Notwithstanding the fact that the serum concentrations differed significantly between groups, statistical analysis revealed only a slight influence of androgens on desire and frequency of sexual contact [8].

Breast cancer survivors

When considering sexual function in female breast cancer survivors who go on to suffer from POI, significant impairment in physical and mental wellbeing is noted when compared to healthy women in the same age range. Vasomotor symptoms (such as night sweats and hot flushes) and vaginal dryness particularly affect women after chemotherapy. A study of 288 women who

underwent gonadotoxic therapy due to malignancy revealed that 35% of those patients went on to develop gonadal failure. The severity of menopausal symptoms (assessed using FACT-ES questionnaire) in women following POI is associated with decreased pleasure and discomfort during intercourse. Similar responses were not observed in patients following chemotherapy, who did not develop impaired gonadal function [16]. Chemotherapy, it would appear, has an influence on the sexual activity of women with POI primarily as a result of the physical changes it induces. Psychological issues, such as decreased libido, lack of sexual interest, and problems with partners, are generally less important factors influencing their sexual life [10].

Ovarian insufficiency following treatment with gonadotoxic chemotherapy is abrupt and irreversible, leading to permanent and usually more pronounced dysfunction. In contrast, patients treated with aromatase inhibitors and GnRH agonists also suffer from vaginal dryness and dyspareunia during administration, but these symptoms are reversible after treatment withdrawal [17]. Tamoxifen seems to decrease sexual fear, have a positive influence on sexual activity, and ameliorate the negative effect of GnRH agonists on the sexual life of patients treated for breast cancer [18].

Treatment

Lifestyle modifications and smoking cessation are important but usually insufficient components in the treatment of sexual impairment in POI patients. When psychology is suspected as the underlying cause of sexual problems, intervention programs and counselling may be beneficial. Additionally, vaginal moisturisers, water- or silicone-based lubricants, and pelvic floor muscle exercises can also be beneficial, especially in addressing vaginal dryness and dyspareunia. Although these are good alternatives for patients with contraindications for hormonal treatment, they do not treat the underlying issues and thus provide only temporary relief [19, 20].

Systemic hormone replacement therapy

The primary basis of POI treatment is hormonal, oestroprogestative therapy until the average age of natural menopause in the population. Sex life dysfunction is noted in POI, regardless of hormonal therapy. Recently conducted studies indicate that when considering the domains of sexual life (evaluated by FSFI questionnaire), no difference was noted between POI patients who underwent hormonal replacement therapy and those who did not [9]. Yela *et al.* observed that independently of oestroprogestative hormone therapy, POI patients presented similar dysfunctions of sexual life, and showed a similar association between sexual impairment and quality of life [13]. In another study, Pacello *et al.* reported that patients suffering from POI undergoing hormone replacement therapy (HRT) had worse sexual performance in all domains documented by FSFI questionnaire compared to healthy, age-matched controls. They conclude HRT to be inefficient in adequately restoring sexual function [5]. Systemic HRT was also insufficient in restoring adequate mucosa nutrition. Nevertheless, oestradiol with norethisterone, and conjugated oestrogen plus medroxyprogesterone acetate, were found to adequately restore the vaginal flora to levels seen in healthy controls [5]. Therefore, systemic HRT is usually accompanied by topical oestrogens.

Ospemifene

Ospemifene is an alternative for breast-cancer survivors suffering from vulvar atrophy. As a non-hormonal selective oestrogen receptor modulator, it exerts nearly a full oestrogen agonist effect in the vaginal epithelium without increasing the concentration of oestradiol in the serum. It is therefore an established treatment for vulvar and vaginal atrophy associated with moderate to severe dyspareunia. Ospemifene is a safe alternative for patients with a history of breast cancer, particularly following anti-oestrogen activity in breast tissue [21].

Androgens

It is known that the decreased concentration of androgens seen in POI patients is associated with sexual impairment. Therefore, restoring adequate concentration of androgens may be beneficial in alleviating sexual problems in this patient group. In the study from 2010, Paney *et al.* demonstrated that a transdermal administration of testosterone at a dose of 300 µg/day increased the total number of satisfying sexual episodes in postmenopausal patients suffering from HSDD. Moreover, patients demonstrated significantly higher desire and reduced personal distress when compared to a placebo group. Discontinuation of treatment due to the presence of mild to moderate adverse effects was considered the main limitation, but it was nevertheless was reported in both groups without statistically significant difference [22].

Topical therapy

Local oestrogen therapy can be prescribed to patients suffering from vaginal dryness and decreased lubrication during intercourse. Evidence has accumulated indicating that topical administration of oestrogens restores vaginal cytology and vaginal flora, increases vaginal fluid secretions and blood flow, as well as de-

creases vaginal pH [23]. Nevertheless, recent studies have reported that the topical route of administration may lead to an increase of oestrogen serum concentration. Such an effect may negatively impact the clinical outcomes of patients with a history of oestrogen-dependent cancer [21].

Disclosure

The authors report no conflict of interest.

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